

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00		A1	(11) International Publication Number: WO 96/19968
			(43) International Publication Date: 4 July 1996 (04.07.96)
(21) International Application Number: PCT/EP95/05085 (22) International Filing Date: 22 December 1995 (22.12.95) (30) Priority Data: 9426252.4 24 December 1994 (24.12.94) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): GREEN, Alexander, Peter [GB/GB]; Glaxo Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP (GB). (74) Agent: GALLAFENT, Alison; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).			(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL AEROSOL CONTAINING AT LEAST ONE SUGAR			
(57) Abstract This invention relates to aerosol formulations of use for the administration of medicaments by inhalation and in particular to a pharmaceutical aerosol formulation which comprises (a) particulate medicament; (b) at least one sugar; and (c) a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation as defined is also described.			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PHARMACEUTICAL AEROSOL CONTAINING AT LEAST ONE SUGAR

This invention relates to aerosol formulations of use for the administration of medicaments by inhalation.

5

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol. The most commonly used aerosol propellants for medicaments have been propellant 11 (CCl_3F) and/or propellant 114 ($\text{CF}_2\text{ClCF}_2\text{Cl}$) with propellant 12 (CCl_2F_2). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

15

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise fluorocarbons and hydrogen-containing chlorofluorocarbons, and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, WO91/04011, WO91/11173, WO91/11495 and WO91/14422. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications all propose the addition of one or more of adjuvants such as alcohols, alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc) and even conventional chlorofluorocarbon propellants in small amounts intended to minimise potential ozone damage.

25
30

Surprisingly, the applicants have now found that particular sugars may advantageously be used to prepare novel aerosol formulations.

Thus, one aspect of the invention provides an aerosol formulation comprising:

35

- a) particulate medicament;
- b) at least one sugar; and

c) a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

5 In an alternative embodiment the present invention provides a pharmaceutical aerosol formulation as hereinbefore defined with the provisos that when said formulation consists essentially of human insulin, soybean lecithin S100, lactose and heptafluoropropane the weight to weight ratio of medicament to lactose is other than 1:1 and that when said formulation consists essentially of salbutamol, soybean lecithin S100, lactose and heptafluoropropane the weight to weight ratio of medicament to lactose is other than 200:1798.

10 The particle size of the particulate (e.g. micronised) medicament should be such as to permit substantially all of the particles to be potentially available for inhalation into the lungs upon administration of the powder composition. Thus, for example, at least 90%, preferably at least 95% by weight of the particles will have a diameter of less than 15 micrometres, preferably in the range of 1 to 10 micrometres, for example 1 to 5 micrometres.

15 The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 - 5% w/w, especially 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

20 Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy and which may be presented in a form which is substantially completely insoluble in the selected propellant. Appropriate medicaments may thus be selected from, for example, 25 analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. 30 methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tulobuterol, 35 orciprenaline, or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g.

ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where
5 appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

10 Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include antiallergics, bronchodilators and antiinflammatory steroids of use in the treatment of respiratory disorders such as asthma by inhalation therapy, for example cromoglycate (e.g. as the sodium
15 salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclomethasone ester (e.g. the dipropionate), a fluticasone ester (e.g. the propionate) or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol. Salmeterol, especially
20 salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the aerosol formulations
25 according to the invention may, if desired, contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients (in a conventional propellant system) are known, for example, for the treatment of respiratory disorders such as asthma. Accordingly the present invention further provides aerosol formulations in accordance with the invention which contain
30 two or more particulate medicaments. Thus suitable combinations of bronchodilatory agents include ephedrine and theophylline, fenoterol and ipratropium, and isoetharine and phenylephrine aerosol formulations.

Preferred aerosol formulations in accordance with the invention comprise (a) an
35 effective amount of a particulate bronchodilatory medicament, (b) an effective amount of a particulate antiinflammatory, preferably a steroidal antiinflammatory

medicament, (c) a fluorocarbon or hydrogen - containing chlorofluorocarbon propellant, and (d) at least one sugar. Particularly preferred aerosol formulations contain bronchodilators such as salbutamol (e.g. as the free base or as the sulphate salt), salmeterol (e.g. as the xinafoate salt) or isoprenaline in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g. the dipropionate) or a fluticasone ester (e.g. the propionate). Alternatively aerosol formulations may contain a bronchodilator in combination with an antiallergic such as cromoglycate (e.g. the sodium salt). Combinations of isoprenaline and sodium cromoglycate, salmeterol and fluticasone propionate, or salbutamol and beclomethasone dipropionate are especially preferred.

The aerosol formulations according to the present invention desirably contain 0.0001 to 50% w/w, preferably 0.001 to 20, for example 0.001 to 1% of sugar relative to the total weight of the formulation. Generally the ratio of medicament : sugar falls within the range of 1:0.01 to 1:100 preferably 1:0.1 to 1:10.

The particle size of the sugars used in the formulations of the present invention can be selected as desired using conventional techniques such as milling or micronisation. However, preferably the sugars will have a particle size of less than about 100 microns such as less than about 70 microns, for example, less than 20 microns. Typical sugars which may be used in the formulations include, for example, sucrose, lactose and dextrose, preferably lactose, and reducing sugars such as mannitol and sorbitol..

The propellants for use in the invention may be any fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Preferably the propellant will be a non-solvent for the medicament. Suitable propellants include, for example, C₁₋₄hydrogen-containing chlorofluorocarbons such as CH₂ClF, CCIF₂CHClF, CF₃CHClF, CHF₂CCIF₂, CHClFCHF₂, CF₃CH₂Cl and CCIF₂CH₃; C₁₋₄hydrogen-containing fluorocarbons such as CHF₂CHF₂, CF₃CH₂F, CHF₂CH₃ and CF₃CHF₂CF₃; and perfluorocarbons such as CF₃CF₃ and CF₃CF₂CF₃.

Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chlorofluorocarbons for example CHClF_2 , CH_2F_2 and CF_3CH_3 . Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C_{1-4} hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane($\text{CF}_3\text{CH}_2\text{F}$) and 1,1,1,2,3,3,3-heptafluoro-n-propane ($\text{CF}_3\text{CHFCF}_3$).

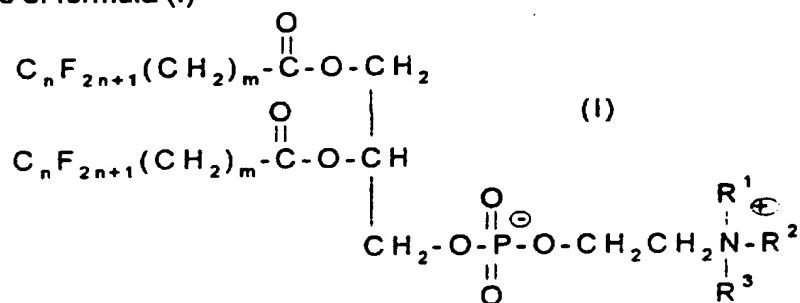
It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F , CCl_2F_2 and CF_3CCl_3 .

The propellant may optionally contain an adjuvant having a higher polarity and/or a higher boiling point than the propellant. Polar adjuvants which may be used include (e.g. C_{2-6}) aliphatic alcohols and polyols such as ethanol, isopropanol and propylene glycol, preferably ethanol. In general only small quantities of polar adjuvants (e.g. 0.05 - 3.0% w/w based upon the propellant) may be required to improve the stability of the dispersion - the use of quantities in excess of 5% w/w may tend to dissolve the medicament. Formulations in accordance with the invention may preferably contain less than 1% w/w, e.g. about 0.1% w/w, of polar adjuvant. However, the formulations of the invention are preferably substantially free of polar adjuvants, especially ethanol. Suitable volatile adjuvants include saturated hydrocarbons such as propane, n-butane, isobutane, pentane and isopentane and alkyl ethers such as dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile adjuvant, for example 1 to 30% w/w of a volatile saturated C_{1-6} hydrocarbon.

Optionally, the aerosol formulations according to the invention may further comprise one or more surfactants. The surfactants must be physiologically acceptable upon administration by inhalation. Within this category are included surfactants such as oleic acid, sorbitan trioleate (Span^R 85), sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl

polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil. Preferred surfactants are lecithin, oleic acid and sorbitan trioleate.

- 10 An alternative class of surfactants are described in EP 0478686, especially surfactants of formula (I)



- 15 wherein n is an integer of 1 to 18, especially 2 to 12; m is an integer of 0 to 17, especially 0 to 11; and R^1 , R^2 and R^3 are each independently a hydrogen atom or a C_{1-4} alkyl group.

- 20 Particularly preferred surfactants of formula (I) are the fluorinated phosphatidylcholines wherein R^1 , R^2 and R^3 each represent methyl, n is an integer of 4 to 8, especially 4 or 6, and m is an integer of 4 to 10, especially 4 or 6.

- 25 If desired, the surfactant may be incorporated into the aerosol formulation in the form of a surface coating on the particulate medicament. In this case, the use of substantially non-ionic surfactants which have reasonable solubility in substantially non-polar solvents is frequently advantageous since it facilitates coating of the medicament particles using solutions of surfactant in non-polar solvents in which the medicament has limited or minimal solubility.

The amount of surfactant employed in coating the particulate medicament is desirably in the range 0.1 to 10% w/w, preferably 1 to 10% w/w, relative to the medicament. Where the surfactant is present as a surface coating, the amount may advantageously be chosen such that a substantially monomolecular coating of surfactant is formed. However, it is preferable that the formulations of the invention are substantially free of surfactants, i.e contain less than an effective stabilising amount of a surfactant such as less than 0.0001% by weight of medicament.

The formulations according to the present invention may optionally contain one or more further excipients or carriers conventionally used in the art of pharmaceutical aerosol formulation. Such optional excipients include, but are not limited to, taste masking agents, buffers, antioxidants, water and chemical stabilisers.

A particularly preferred embodiment of the invention provides a pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament, particulate lactose and one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

The formulations of the invention may be prepared by dispersal of the medicament and sugar e.g lactose in the selected propellant in an appropriate container, e.g. with the aid of mixing. Alternatively, the sugar may be pre-filled into canisters suitable for delivering aerosol formulations before filling with the medicament in the selected propellant. The process is desirably carried out under anhydrous conditions to obviate any adverse effects of moisture on suspension stability.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by

dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

5 The suspension stability of the aerosol formulations according to the invention is particularly impressive and may be measured by conventional techniques, for example by measuring flocculation size distribution using a back light scattering instrument or by measuring particle size distribution by cascade impaction or by the "twin impinger" analytical process. As used herein reference to the "twin
10 impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopoeia 1988, pages A204-207, Appendix XVII C.

15 The formulations according to the invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. The metering valves are designed to deliver a metered amount of the
20 formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in
25 the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bepak plc, UK (e.g. BK300, BK357) and 3M-Neotechnic Ltd, UK (e.g. SpraymiserTM).

30 Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The particulate medicament and sugar may or may not be pre-blended and then
35 added to one or more charge vessels. Liquified propellant is pressure-filled through the charge vessel(s) into a manufacturing vessel. The medicament and

sugar suspension is mixed before recirculation to a filling machine and an aliquot of the medicament and sugar suspension is then filled through the metering valve of the canister.

- 5 Alternatively the sugar may be mixed with the selected propellant in a suitable vessel and then added to the canister either before or after the medicament suspension is added to the canister.

- 10 Alternatively, the sugar and optionally the medicament may be pre-filled into the empty canisters before the propellant is filled into the canisters.

- 15 Alternatively, the sugar may be coated onto the empty canisters by dissolving or dispersing the sugar in a suitable liquid, for example a solvent for the sugar such as water or methanol, or a non-solvent for the sugar such as acetone or hexane, and adding to the empty canister. After orientation to ensure that the solution or dispersion covers the interior surfaces of the canister, the liquid may be evaporated off leaving a coat of sugar on the interior surfaces of the canister. The canister is then filled with medicament in the selected propellant.

- 20 Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

- 25 Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channelling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose
30 inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

- 35 Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age

and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time.

Suitable daily doses, may be, for example in the range 50 to 200 microgram of salmeterol, 100 to 1000 microgram of salbutamol, 50 to 2000 microgram of fluticasone propionate or 100 to 2000 microgram of beclomethasone dipropionate, depending on the severity of the disease.

Thus, for example, each valve actuation may deliver 25 microgram salmeterol, 100 microgram salbutamol, 25, 50, 125 or 250 microgram fluticasone propionate or 50, 100, 200 or 250 microgram beclomethasone dipropionate. Typically each filled canister for use in a metered dose inhaler contains 50, 80, 100, 120, 160 or 240 metered doses or puffs of medicament.

The filled canisters and metered dose inhalers described herein comprise further aspects of the present invention.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of a formulation as herein described.

The following non-limitative Examples serve to illustrate the invention.

Example 1

Particulate lactose was dispensed into clean, dry glass bottle. The metering valve was fitted onto the bottles and micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled into the canisters through the metering valve. The resultant inhalers delivered 25 microgram of fluticasone

propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:10. The proportion of lactose was 0.33% of the total fill weight of the inhaler.

Example 2

5

Particulate lactose was dispensed into clean, dry aluminium aerosol canisters. The metering valve was fitted onto the canisters and micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled into the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then
10 pressure-filled into the canisters through the metering valve. The resultant inhalers delivered 50 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:1. The proportion of lactose was 0.067% of the total fill weight of the inhaler.

15

Example 3

Particulate lactose was dispensed into clean, dry aluminium aerosol canisters. The metering valve was fitted onto the canisters and micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled into the
20 canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled into the canisters through the metering valve. The resultant inhalers delivered 50 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.33% of the total fill weight of the inhaler.

25

Example 4

Particulate lactose and micronised fluticasone propionate were mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters
30 fitted with a metering valve. 1,1,1,2-Tetrafluoroethane was then pressure filled into the canisters through the metering valve. The resultant inhalers delivered 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.167% of the total fill weight of the inhaler.

35

Example 5

Particulate lactose and micronised fluticasone propionate were mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters fitted with a metering valve. 1,1,1,2-Tetrafluoroethane was then pressure filled into the canisters through the metering valve. The resultant inhalers delivered 50 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:1. The proportion of lactose was 0.067% of the total fill weight of the inhaler.

Example 6

Particulate lactose and micronised fluticasone propionate were mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters fitted with a metering valve. 1,1,1,2-Tetrafluoroethane was then pressure filled into the canisters through the metering valve. The resultant inhalers delivered 50 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.333% of the total fill weight of the inhaler.

Example 7

Particulate lactose and micronised fluticasone propionate were mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters fitted with a metering valve. 1,1,1,2-Tetrafluoroethane was then pressure filled into the canisters through the metering valve. The resultant inhalers delivered 50 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:8. The proportion of lactose was 0.533% of the total fill weight of the inhaler.

Example 8

Particulate lactose and micronised fluticasone propionate were mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters fitted with a metering valve. 1,1,1,2-Tetrafluoroethane was then pressure filled into the canisters through the metering valve. The resultant inhalers delivered

25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.167% of the total fill weight of the inhaler.

5 Example 9

Particulate lactose was dispensed in to clean, dry aluminium aerosol canisters. The metering valve was fitted on to the canisters and micronised salmeterol xinafoate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled in to the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled in to the canisters through the metering valve. The resultant inhalers delivered 25 microgram of salmeterol (ex-valve) per actuation. The ratio of medicament : lactose was 1:1. The proportion of lactose was 0.053% of the total fill weight of the inhaler.

15 Example 10

Particulate lactose was dispensed in to clean, dry aluminium aerosol canisters. The metering valve was fitted on to the canisters and micronised salmeterol xinafoate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled in to the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled in to the canisters through the metering valve. The resultant inhalers delivered 25 microgram of salmeterol (ex-valve) per actuation. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.266% of the total fill weight of the inhaler.

25 Example 11

Particulate sucrose was dispensed in to clean, dry aluminium aerosol canisters. The metering valve was fitted on to the canisters and micronised salmeterol xinafoate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled in to the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled in to the canisters through the metering valve. The ratio of medicament : sucrose was 1:1. The proportion of sucrose was 0.266% of the total fill weight of the inhaler.

Example 12

Particulate dextrose was dispensed in to clean, dry aluminium aerosol canisters. The metering valve was fitted on to the canisters and micronised salmeterol xinafoate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled in to the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled in to the canisters through the metering valve. The ratio of medicament : dextrose was 1:5. The proportion of dextrose was 0.266% of the total fill weight of the inhaler.

Example 13

Particulate mannitol was dispensed in to clean, dry aluminium aerosol canisters. The metering valve was fitted on to the canisters and micronised salmeterol xinafoate, mixed with 1,1,1,2-tetrafluoroethane was pressure-filled in to the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane was then pressure-filled in to the canisters through the metering valve. The ratio of medicament : mannitol was 1:5. The proportion of mannitol was 0.266% of the total fill weight of the inhaler.

Example 14

Particulate lactose is blended with salmeterol xinafoate and the blend is mixed with 1,1,1,2-tetrafluoroethane and pressure-filled in to clean, dry aluminium canisters fitted with a metering valve, through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressured-filled in to the canisters through the metering valve. The ratio of medicament : lactose was 1:1. The proportion of lactose was 0.053% of the total fill weight of the inhaler.

Example 15

Particulate lactose is blended with salmeterol xinafoate and the blend is mixed with 1,1,1,2-tetrafluoroethane and pressure filled in to clean, dry aluminium canisters fitted with a metering valve, through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressured-filled in to the canisters through the

metering valve. The ratio of medicament : lactose was 1:5. The proportion of lactose was 0.266% of the total fill weight of the inhaler.

Example 16

5

Particulate lactose is blended with salmeterol xinafoate and the blend is mixed with 1,1,1,2-tetrafluoroethane and pressure-filled in to clean, dry aluminium canisters fitted with a metering valve, through the metering valve. 1,1,1,2-tetrafluoroethane is then pressured-filled in to the canisters through the metering valve. The ratio of medicament : lactose was 1:10. The proportion of lactose was 0.532% of the total fill weight of the inhaler.

10

Example 17

15

Particulate lactose is blended with micronised fluticasone propionate and the blend is mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into clean, dry aluminium canisters fitted with a metering valve, through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressure-filled into the canisters through the metering valve. The resultant inhalers deliver 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose is 1:1. The proportion of lactose is 0.033% of the total fill weight of the inhaler.

20

Example 18

25

Particulate lactose is mixed with 1,1,1,2-tetrafluoroethane and added to clean, dry aluminium aerosol canisters fitted with a metering valve. Micronised fluticasone propionate is mixed with 1,1,1,2-tetrafluoroethane and pressure-filled into the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressure-filled into the canisters through the metering valve. The resultant inhalers deliver 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose is 1:1. The proportion of lactose is 0.033% of the total fill weight of the inhaler.

30

35

Example 19

Particulate lactose is dispensed into clean, dry aluminium aerosol canisters. The metering valve is fitted onto the canisters and micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane is pressure-filled into the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressure-filled into the canisters through the metering valve. The resultant inhalers deliver 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose is 1:1. The proportion of lactose is 0.033% of the total fill weight of the inhaler.

Example 20

Particulate lactose is dissolved in water/ethanol/methanol or a mixture thereof and added to clean, dry aluminium aerosol canisters. The canister is orientated such that the walls are coated with the solution. The solvent is evaporated off leaving a coating of lactose on the walls of the canister. Micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane is pressured-filled into the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressure-filled into the canisters through the metering valve. The resultant inhalers deliver 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose is 1:1. The proportion of lactose is 0.033% of the total fill weight of the inhaler.

Example 21

Particulate lactose is dispersed in a suitable non-solvent for lactose, for example acetone, and added to clean, dry aluminium aerosol canisters. The canister is orientated such that the walls are coated with the dispersion. The non-solvent is evaporated off leaving a coating of lactose on the walls of the canister. Micronised fluticasone propionate, mixed with 1,1,1,2-tetrafluoroethane is pressure-filled into the canisters through the metering valve. 1,1,1,2-Tetrafluoroethane is then pressure-filled into the canisters through the metering valve. The resultant inhalers deliver 25 microgram of fluticasone propionate (ex-valve) per actuation. The ratio of medicament : lactose is 1:1. The proportion of lactose is 0.033% of the total fill weight of the inhaler.

Examples 22 - 41

5 Aerosols are prepared as described in Examples 17 to 21 but containing 50 microgram per actuation fluticasone propionate (Examples 22 to 26), salmeterol 25 microgram per actuation (Examples 27 to 31), salbutamol 100 microgram per actuation (Examples 32 to 36) or beclomethasone dipropionate 50 microgram per actuation (Examples 37 to 41) in place of fluticasone propionate.

10 Examples 42 - 46

Aerosols are prepared as described in Examples 17 to 21 but with 1:5 ratio of medicament : lactose. The proportion of lactose is 0.167% of the total fill weight of the inhaler.

15

Examples 47 - 51

Aerosols are prepared as described in Examples 17 to 21 but with 1:10 ratio of medicament : lactose. The proportion of lactose is 0.33% of the total fill weight of the inhaler.

20

Examples 52 - 56

Aerosols are prepared as described in Examples 17 to 21 but with 1:0.1 ratio of medicament : lactose. The proportion of lactose is 0.0033% of the total fill weight of the inhaler.

25

Examples 57 - 104

Aerosols are prepared as described in Examples 42 to 56 but containing 50 microgram per actuation fluticasone propionate (Examples 57 to 72), 25 microgram per actuation salmeterol (Examples 73 to 88) and 100 microgram per actuation salbutamol (Examples 89 to 104).

35

Examples 105 - 129

- 5 Aerosols are prepared as described in Examples 17 to 41 but containing 1,1,1,2,3,3,3-heptafluoro-n-propane as propellant in place of 1,1,1,2-tetrafluoroethane.

Examples 130 - 144

- 10 Aerosols are prepared as described in Examples 7 to 21 but containing dextrose (Examples 130 to 134), sucrose (Examples 135 to 139) or mannitol (Examples 140 to 144) in place of lactose.

CLAIMS

1. A pharmaceutical aerosol formulation comprising
 - (a) particulate medicament;
 - 5 (b) at least one sugar; and
 - (c) a fluorocarbon or hydrogen - containing chlorofluorocarbon propellant.
2. A pharmaceutical aerosol formulation comprising
 - (a) particulate medicament;
 - 10 (b) at least one sugar; and
 - (c) a fluorocarbon or hydrogen - containing chlorofluorocarbon propellant, with the proviso that when said formulation consists essentially of human insulin, soybean lecithin S100, lactose and heptafluoropropane the weight to weight ratio of medicament to lactose is other than 1:1 and that when said
 - 15 formulation consists essentially of salbutamol, soybean lecithin S100, lactose and heptafluoropropane the weight to weight ratio of medicament to lactose is other than 200:1798.
3. A formulation according to claim 1 or claim 2 comprising 0.0001 to 50%
20 w/w of sugar relative to the total weight of the formulation.
4. A formulation according to claim 3 comprising 0.001 to 20% w/w of sugar relative to the total weight of the formulation.
- 25 5. A formulation according to any one of claims 1 to 4 wherein the propellant comprises 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof.
6. A formulation according to any one of claims 1 to 5 wherein the
30 medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.
7. A formulation according to any one of claims 1 to 6 wherein the medicament is salmeterol xinafoate.

8. A formulation according to any one of claims 1 to 6 wherein the medicament is salbutamol sulphate.

5 9. A formulation according to any one of claims 1 to 6 wherein the medicament is fluticasone propionate.

10 10. A formulation according to any one of claims 1 to 6 wherein the medicament is beclomethasone dipropionate of a physiologically acceptable solvate thereof.

11. A formulation according to any one of claims 1 to 6 wherein the medicament is formoterol, cromoglycate, terbutaline, reproterol or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzylmethanol budesonide, triamcinolone acetonide or a physiologically acceptable salt or solvate thereof.

12. A formulation according to any one of claims 1 to 11 wherein the medicament is present in an amount of 0.005 to 10% w/w relative to the total weight of the formulation.

13. A formulation according to claim 12 wherein the medicament is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

14. A formulation according to any one of claims 1 to 13 which contains two or more particulate medicaments.

15. A formulation according to claim 14 which contains salbutamol or salmeterol or a physiologically acceptable salt thereof in combination with an anti-inflammatory steroid or an anti-allergic.

16. A formulation according to claim 15 which contains salmeterol or salbutamol or a physiologically acceptable salt thereof in combination with fluticasone propionate or beclomethasone dipropionate or a physiologically acceptable solvate thereof.

17. A formulation according to any one of claims 1 to 16 comprising an adjuvant having a higher polarity and/or a boiling point than the propellant.

18. A formulation according to claim 17 wherein the adjuvant having a higher polarity than the propellant is present in an amount of 0.05 to 5% w/w based upon the propellant.

19. A formulation according to any one of claims 1 to 18 comprising a surfactant.

20. A formulation according to any one of claims 1 and 3 to 18 wherein said formulation is substantially free of surfactant.

21. A canister suitable for delivering a pharmaceutical aerosol formulation which comprises a container capable of withstanding the vapour pressure of the propellant used which container is closed with a metering valve and contains a pharmaceutical aerosol formulation according to any one of claims 1 to 20.

22. A canister according to claim 21 wherein the container is a metal can.

23. A canistrer according to claim 22 wherein the container is an aluminium can.

24. A canister according to claim 22 or 23 wherein the container is plastics-coated.

25. A metered dose inhaler which comprises a canister according to any one of claims 21 to 24 fitted into a suitable channelling device.

26. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation according to any one of claims 1 to 20.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/05085

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A51K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A51K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 561 166 (ASTA MEDICA AKTIENGESELLSCHAFT) 22 September 1993	1,3-6, 12,13, 17-19, 21-25
Y	see page 4; example 1 see page 2, line 1 - line 20 ---	14
Y	EP,A,0 423 695 (STERLING DRUG INC.) 24 April 1991 see claims 1-4 see page 2, line 44 - page 3, line 5 -----	14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 March 1996

Date of mailing of the international search report

22.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

national application No.

PCT/EP 95/05085

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 26 is directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC./EP 95/05085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-561166	22-09-93	AU-B- 3526193	23-09-93
		BR-A- 9301172	21-09-93
		CA-A- 2091713	18-09-93
		DE-A- 4305078	23-09-93
		JP-A- 6016539	25-01-94
		ZA-A- 9301875	06-10-93

EP-A-423695	24-04-91	AU-B- 6463490	26-04-91
		CA-A- 2027952	20-04-91
		JP-A- 3255023	13-11-91
		US-A- 5378451	03-01-95

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.